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Long-Lasting Ibogaine Protection against NMDA-Induced Convulsions in Mice

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Ibogaine, a putative antiaddictive drug, is remarkable in its apparent ability to downgrade withdrawal symptoms and drug craving for extended periods of time after a single dose. Ibogaine acts as a non-competitive NMDA receptor antagonist, while NMDA has been implicated in long lasting changes in neuronal function and in the physiological basis of drug addiction. The purpose of this study was to verify if persistent changes in NMDA receptors could be shown in vivo and in vitro after a single administration of ibogaine. The time course of ibogaine effects were examined on NMDA-induced seizures and [³H] MK-801 binding to cortical membranes in mice 30min, 24, 48, and 72h post treatment. Ibogaine (80 mg/kg, ip) was effective in inhibiting convulsions induced by NMDA at 24 and 72 hours post administration. Likewise, [³H] MK-801 binding was significantly decreased at 24 and 72 h post ibogaine. No significant differences from controls were found at 30min or 48h post ibogaine. This long lasting and complex pattern of modulation of NMDA receptors prompted by a single dose of ibogaine may be associated to its antiaddictive properties.

KEY WORDS: Ibogaine; [³H] MK-801 binding; NMDA; NMDA-induced convulsions.

INTRODUCTION

Ibogaine is an indole alkaloid extracted from *Tabernanthe iboga* with putative antiaddictive properties. A remarkable aspect of this drug is its apparent ability to eliminate withdrawal symptoms and drug craving for extended periods of time after a single dosage, as indicated by anecdotal reports and uncontrolled clinical data (1–3). These reports are somewhat supported by animal studies (4–10). Ibogaine presents a complex mechanism of action, altering various neurotransmitter systems, including

serotonergic, dopaminergic, opioid, nicotinic, and glutamatergic (10–17).

Glutamate, the main excitatory neurotransmitter in the mammalian central nervous system (CNS), is believed to play important roles in several physiological and pathological processes. Glutamatergic neurotransmission is achieved through ionotropic (ligand-gated ion channel) and metabotropic (coupled to cellular effectors) receptors (18). Specifically, the N-methyl-D-aspartate (NMDA) ionotropic glutamate receptor subtype seems to be crucial in plastic changes associated with normal brain function (as in learning and memory), in neurodegenerative diseases and epilepsy (19–23), as well as in drug addiction (24,25). In fact, NMDA antagonists have been explored as potential anticonvulsant, neuroprotective and antiaddictive drugs (20,21,26). Pre clinical data have consistently indicated that NMDA antagonists interfere with sensitization, tolerance and/or dependence induced by stimulants, nicotine, alcohol, benzodiazepine, barbiturates, and morphine (24,26–35). Ibogaine interferes with

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the glutamatergic system, acting as a noncompetitive NMDA receptor antagonist, inhibiting [^3H]MK-801 and [^3H]TCP binding to NMDA receptors (17,36–41).

Considering that long lasting changes in neuronal function related to NMDA receptors are thought to be associated with drug addiction as well as with epileptic phenomena, the antiepileptic profile of ibogaine is of interest. Ibogaine has been shown to suppress electrically (42) or pentylenetetrazol (PTZ)-induced tonic seizures in mice (43), but found to be ineffective in suppressing strychnine- or caffeine-induced tonic seizures (43). Moreover, ibogaine partially protects mice against NMDA-induced convulsions (44) or lethality (42).

In order to further scrutinize the participation of NMDA receptors in the long lasting effects of ibogaine, we here report the time course of ibogaine effects in mice. The effects of a single administration of ibogaine were examined by evaluating the protection against NMDA-induced convulsions and on [^3H]MK-801 binding to cortice membranes at different periods post treatment.

EXPERIMENTAL PROCEDURE

Animals. Male albino adult (25–35g) mice (CF-1 strain), bred at the Fundação Estadual de Produção e Pesquisa em Saúde (Porto Alegre, RS, Brazil), were used in all experiments. Mice were kept on a 12 light/dark cycle, at a room temperature of 22°C, with free access to food and water. All procedures were carried out according to institutional policies on animal experimental handling.

Drugs. N- Methyl-D-Aspartate (NMDA) and glycine were purchased from Sigma (St. Louis, MO, USA), (+) MK-801 hydrogen maleate was purchased from RBI (Natick, MA, USA), [^3H]MK-801 (22.5 Ci/mmol) was purchased from Du-Pont-NEN (Boston, MA, USA), glutamic acid was purchased from Merck (Darmstadt, Germany). Ibogaine hydrochloride was kindly donated by Howard Lotsof (NDA Int. Inc., USA). All other reagents were of analytical grade. Drugs were dissolved in milli-Q water.

Behavioral Experiments

NMDA-Induced Seizures. The method of Czuczwar et al (45) was adapted as follows. Ibogaine (60 and 80 mg/kg) or saline were injected intraperitoneally (ip) 30 min and 24 h before subcutaneous (sc) NMDA (240 mg/kg). Additional groups were treated with ibogaine (80 mg/kg) 48 and 72 h before NMDA. After receiving NMDA, animals were individually placed in plexiglas boxes (20×20×20 cm) and observed during 60 min for the occurrence of continuous clonic seizures lasting at least 3 seconds, with loss of righting reflex. Results are expressed as the percentage of seizuring animals. Data were analyzed by means of the Fisher exact probability test.

Rota-Rod Performance in Mice. Mice were initially trained to remain on the rota-rod apparatus (18 rpm) for 120 sec; those that did not remain on the bar for at least two out of three consecutive trials were discarded (46). Ibogaine (60 and 80 mg/kg) or saline were administered ip 24 h after this initial training. The latency to fall from the rotarod (one trial of maximum 60 sec) was determined 30, 60, 90, 120 min, and 24, 48, and 72 h after administration of saline or ibogaine. Latency

results are expressed as mean $\pm$ SEM. Results were analyzed by means of ANOVA followed by a Duncan test.

Neurochemistry

Membrane Preparation. Membranes were prepared as described by Emanuelli et al. (47). Thirty min, 24, 48 and 72 hours after treatment (ip, ibogaine 60 and 80 mg/kg or saline), mice were decapitated, and brains rapidly removed; whenever brains were removed a control group was included consisting of brains of naive (non treated) mice. Each membrane preparation consisted of the pooled brains from two equally treated mice. Cerebral cortice were dissected and homogenized (20:1 v:w) in 0.32 M sucrose containing 10 mM Tris/HCl buffer, pH 7.4, and 1 mM MgCl_2 . All steps were carried out at 4°C. The homogenate was centrifuged twice at 1,000 g for 15 min and the final pellet discarded. Both supernatants were pooled and centrifuged at 27,000 g for 15 min. The resulting pellet was lysed in 20 volumes of 5 mM Tris/HCl buffer, pH 7.4 for 30 min, and centrifuged at 27,000 g for 15 min. This pellet was washed three times with lysing buffer (20:1 v:w) by centrifuging at 27,000 g for 15 min. The final pellet was frozen at -70°C for at least 24 h. On the day of binding assay, the membranes were rapidly thawed in a water bath (37°C), homogenized with 3 volumes of 5 mM Tris/HCl, pH 7.4, and centrifuged at 27,000 g for 15 min. The resulting pellet was resuspended in the same buffer, pre-incubated at 37°C for 30 min and centrifuged at 27,000 g for 15 min. The pellet was washed three times in 3 volumes of 5 mM Tris/HCl, pH 7.4, and centrifuged at 27,000 g for 15 min. The final pellet was resuspended in the same buffer in order to yield a protein concentration of 1–2 mg/ml. Protein concentration was measured according to Lowry et al. (48).

Binding of [^3H]MK-801. Binding assay was based on the method of Piggott et al (49). Membranes (~ 200 μg protein/tube) were incubated in 5 mM Tris/HCl buffer (pH 7.4) at 25°C for 1h, containing 2 nM [^3H] MK-801 in the presence of glutamate (50 μM) and glycine (30 μM), in a final volume of 0.5 ml. Non-specific binding was defined as the binding which occurred in the presence of 34 μM non-radioactive MK-801. After incubation, membranes were filtered (reduced pressure, Whatman GF-B filter prewetted in 5 mM Tris/HCl buffer), and rinsed rapidly three times with 5 ml of ice-cold buffer. The dried filters were deposited in vials and radioactivity measured by scintillation counting. All experiments were performed in triplicate. Results were analyzed by means of ANOVA followed by a Duncan test.

RESULTS

Fig. 1 shows the effects of ibogaine (ip) administered 30 min, 24, 48, and 72 hours before NMDA (sc) on NMDA-induced clonic convulsions. Ibogaine 80 mg/kg (but not 60 mg/kg) afforded significant (50%) protection, when administered 24 or 72 hours before NMDA. Ibogaine was ineffective when given 30 min or 48 hours before NMDA.

Fig. 2 shows the effects of ibogaine on Rotarod performance. Ibogaine 60 and 80 mg/kg produced motor impairment up to 30 min after administration, but not thereafter. No deficits were noted on rotarod performance 24, 48 and 72 h after ibogaine (data not shown).

Fig. 3 presents the effects of ibogaine on [^3H]MK-801 binding to mice cortical membranes. The specific

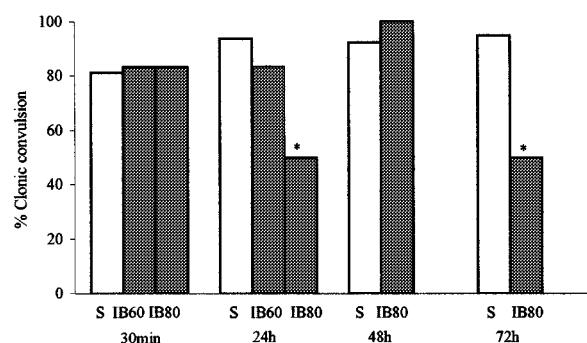


Fig. 1. Effects of saline (S), ibogaine 60 mg/kg (IB60), and 80 mg/kg (IB80), injected ip 30 min, 24 h, 48 h, and 72 h before sc NMDA (240 mg/kg) on NMDA-induced clonic convulsions. (n = 12–20) Data expressed as percentage of mice presenting seizures. * = $p < 0.01$, Fisher Test.

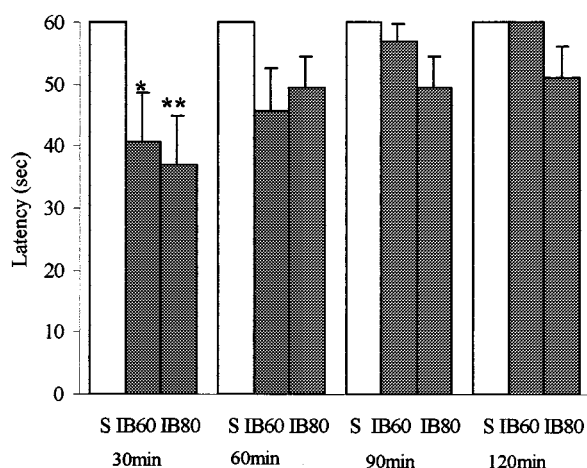


Fig. 2. Effect of saline (S), ibogaine 60 mg/kg (IB60), and 80 mg/kg (IB80), on Rotarod test at 30, 60, 90, and 120 min post treatment. Latency (sec) expressed as mean $\pm$ SEM (n = 8). * = $p < 0.05$ and ** = $p < 0.01$, ANOVA followed by Duncan Test.

[³H]MK-801 binding to cortical membranes of mice after 24 and 72 hours of treatment with 80 mg/kg of ibogaine was significantly decreased in comparison to control (non treated animals) or animals treated with saline.

DISCUSSION

Long lasting changes are expected from ibogaine in humans: the experience that follows the ingestion of a single dose of ibogaine lasts several hours (1,2). The absence of withdrawal symptoms and craving lasting for weeks after ingestion is central to an eventual anti-addictive effect (2,3). In animal models, long lasting effects of

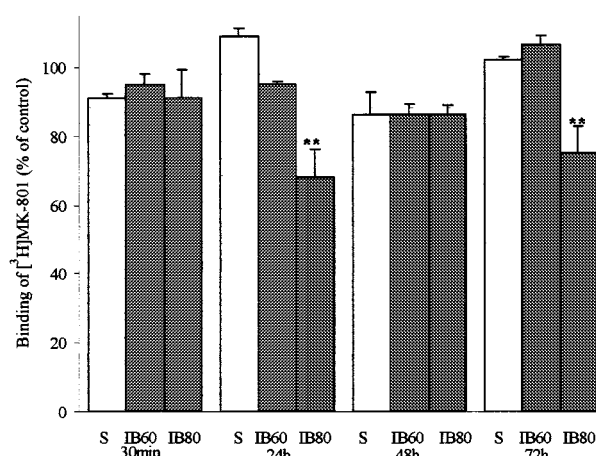


Fig. 3. Effects of saline (S), ibogaine 60 mg/kg (IB 60) and 80 mg/kg (IB 80) on [³H] MK-801 (2 nM) binding in cortical membranes after 30 min, 24, 48, and 72 h post treatment. Data expressed as percentage of binding (0.44 ± 0.03 pmol/mg protein) in non treated animals. Three separate experiments were done in triplicate. (Bars = SEM). * = $p < 0.01$, ANOVA/Duncan.

ibogaine have been previously reported and proved to be dissociated from acute toxicity (4,9,12).

The crucial role of excitatory amino acids (NMDA receptors in particular) in behavioral and neural plasticity has been widely recognized (50,24). The purpose of this study was to verify if long lasting changes in some functional parameters of NMDA receptors could be seen following a single administration of ibogaine. Short and long term effects of ibogaine on NMDA receptors were examined by evaluating NMDA-induced seizures in mice and [³H] MK-801 binding in mice cortical membranes after 30 min, 24, 48, and 72h of treatment with ibogaine.

Ibogaine 60 mg/kg was ineffective in protecting against NMDA-induced convulsions. The administration of 80 mg/kg of ibogaine resulted in 50% protection against NMDA-induced convulsions at 24 and 72 hours post administration. It is noteworthy that the time course of protection afforded by ibogaine against NMDA-induced convulsions, although unusual, correlates well with significant decreases in [³H]MK-801 binding in cortical membranes of mice likewise treated with ibogaine but not subjected to an NMDA challenge.

It was recently reported that 100 mg/kg of ibogaine resulted in 75% protection against NMDA-induced convulsion in mice after 30min of NMDA administration (44). The authors stated that animals treated with this dose presented ataxia and decreased locomotor activity. In our study, no significant protection against convulsions was seen after 30 min or 48 hours of ibogaine 60 or 80 mg/kg. These doses induced temporary tremors but not ataxia. Acute and transient ibogaine toxicity including

nonspecific motor effects (e.g., tremor) are well documented in rats and mice (12). Rotarod results obtained in this study are in agreement with the transient pattern of motor deficits previously reported, with absence of motor deficits after 60 min of ibogaine administration.

Adding to the unique psychoactive profile of ibogaine in non addictive and addictive human subjects (12,16), this study reveals an unusual pattern of activity in an experimental model in mice. There is no simple explanation for the observed pattern of intermittent activity observed in the behavioral and neurochemical parameter evaluated in this study. Since no tissue damage is detected following 100 mg/kg administration of ibogaine to mice (51), the protection afforded by ibogaine 80 mg/kg against NMDA-induced convulsions observed at 24 and 72h is unlikely to result from long term toxicity, in agreement with absence of deficits in the rotarod. Because ibogaine is known to generate noribogaine, a metabolite that also acts as NMDA antagonist, it could be argued that changes triggered by ibogaine itself could be reinforced or maintained by its main metabolite (17,37,38). It is also of relevance to consider ibogaine pharmacokinetics: a sustained and slow release of ibogaine from fat tissue (52) would eventually lead to several hours of constant challenge to NMDA receptors. This pattern of repeated stimulation could lead to significant neural adaptation and consequential long term effects (53). As previously suggested (12), the well known variability in ibogaine effects, both in animals and in humans, may depend both on the extent of fat deposition and on the extent of ibogaine metabolism to noribogaine. Furthermore, NMDA receptors are believed to undergo modifications that lead to or maintain neuroadaptive responses (22). It is possible to postulate that effects observed after 24h of ibogaine treatment are consequent to a direct effect of ibogaine and noribogaine on NMDA receptors, whereas the effects observed after 72 hours could arise from a secondary effect mediated by a cascade of intracellular events leading to an altered expression of NMDA receptors.

This study reports that a single administration of ibogaine induces long lasting effects measurable *in vivo* and *in vitro*. Such results, understood as functional long lasting changes in NMDA receptors, may be relevant within the context of antiaddictive use of ibogaine and NMDA antagonists.

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